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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/905,508	08/04/1997	LALEH SHAYESTEH	02307O-06772	5513

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EXAMINER
ARTHUR, LISA BENNETT

ART UNIT	PAPER NUMBER
1655	20

DATE MAILED: 12/14/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/905,508	Applicant(s) SHAYESTEH ET AL.	
	Examiner Lisa B. Arthur	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This application was filed as a Request for Continued Examination (RCE) on October 5, 2001. Claims 37-39 are pending. All of the amendments and arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. Any rejections which have not been reiterated have been withdrawn.

MAINTAINED REJECTIONS

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential feature of the claimed invention is the correlation between inhibition of PI kinase activity in cells and the resulting inhibition of proliferation of ovarian cancer cells in patients by administration of an inhibitor of PI kinase activity which more specifically is a non-peptidic inhibitor such as LY294002. The specification teaches that increased PI-kinase activity might contribute to tumor progression by increasing the rate of cell proliferation and tested this hypothesis by incubating cells from an ovarian cancer cell line with the known PI-kinase inhibitor

LY294002. The specification teaches that this assay resulted in a significant decrease in cellular proliferation as measured by thymidine incorporation. This decreased proliferation rate was not observed in cells which had normal PIK3CA copy number. The specification states that these studies suggest that therapeutic agents targeting the PI3-kinase pathway may be effective against ovarian cancers. However, the specification does not describe compounds other than LY294002 which inhibit PI-kinase activity such that a common structural feature of a PI-kinase inhibitory compounds was evident to the skilled artisan from the specification. The claims broadly encompass a potentially large genus of compounds which could inhibit PI-kinase activity, but the specification only describes one specific non-peptidic compound and fails to describe any of the structural feature of this compound which are responsible for its function in inhibiting PI-kinase to result in a decrease in cell proliferation of ovarian cells. The specification contains no description of how LY294002 interacts with Pi-kinase to inhibit its activity, such that the skilled artisan would know what other compounds having similar structure and/or function would be. The compounds which are encompassed by this genus of PI-kinase inhibitors appears to be diverse . Minaguchi et al. (CANCER RES. (1999)59:6063-6067) teach that the PTEN gene product encodes a phosphatidylinositol phosphatase which antagonizes the PI-kinase mediated pathway and suggests that overexpression of this gene product could be effective as a therapy for ovarian cancer by inhibiting PI-kinase activity. This inhibitor is structurally very different from that of LY294002 and the specification clearly did not describe such an inhibitor of PI-kinase. However, the inhibitor of Minaguchi et al. would be encompassed by the claims as written. Consequently,

absent a written description disclosing a representative number of species of the PI-kinase inhibitors which function to decrease cell proliferation of ovarian cells, the specification fails to show that applicant was in fact, "in possession of the claimed invention" at the time the application was filed.

Response to Arguments

The response traverses the rejection on the following grounds. The response argues that the invention is not the discovery of PI kinase inhibitors but is instead based upon the discovery that PI kinase plays a role in ovarian cancer proliferation. The response asserts that since PI kinases are well studied and that inhibitors of these enzymes were known, that the inventors recognized that a number of different means for inhibiting PI activity could be used in the invention. This argument has been thoroughly reviewed but is deemed non-persuasive for the following reasons. Claim 37 is drawn to a method for inhibiting ovarian cancer cell proliferation in a patient by administering an effective dose of a compound which inhibits PI kinase enzymatic activity. Consequently, in order to practice this invention the skilled artisan would have to be in possession of compounds which both inhibit PI kinase and which inhibit ovarian cancer cell proliferation. The specification describes one specific compound, LY294002, which inhibited PI kinase activity in ovarian cancer cells *in vitro*. Hu et al.(Clinical Cancer Research (March 2000) 6:880-886) teach that this compounds is a flavanoid derivative and is a competitive, reversible inhibitor of the ATP binding site of PI3-K. Hu et al. Further teach that this compound was already known to induce specific G1 arrest in cell growth leading to inhibition of melanoma cell

proliferation and to partial inhibition of proliferation in an osteosarcoma cell line (Hu et al. Page 880, column 2 , last paragraph). Neither the specification nor the art teach any compound which inhibits kinase activity would be expected to be therapeutically useful. For example, while the specification describes one specific compound and its effect on the growth of ovarian cells in culture, the specification does not describe the structural features of this compound to which its anti-proliferative activity can be attributed such that other compounds with similar structural features would have been obviously part of the invention. Clearly any compound which inhibits the activity of the PI3 kinase will not be effective as a therapeutic for ovarian cancer. Compounds which inhibit kinases in general would not be expected to be effective therapeutics because of their expected inhibition of a number of beneficial kinases. LY294002 is a very specific competitive and reversible inhibitor which can bind and be released from the ATP binding site. This compound is structurally very different from an inhibitor which, for instance, covalently and permanently modifies the kinase to inactivate it and consequently is not representative of the genus of compounds which are claimed in the method. The specification also has not identified a representative number of "non-peptidic" compounds which would be effective as therapeutics because the ability of LY294002 to function as an anti-proliferative agent does not lie in the fact that it is not a peptide but instead its' specific ability to function as a competitive and reversible ATP binding agent to the PI3-K kinase.

The response argues that *in re Fuetterer* established that the particular structure of the inhibitor used is not critical to the invention so long as the desired function is achieved. This

rationale has been thoroughly reviewed but is not convincing because as discussed above the specification has not established that inhibition of PI kinase activity by any means is what makes a compound useful as a therapeutic to inhibit ovarian cancer cell proliferation in a patient. The activity of LY294002, exemplified compound, is much more fine tuned than general inactivation of PI3-K. The description requirements for a method of treating a patient with a therapeutic agent are clearly more complex than for a method of inhibiting growth of a cell in vitro. In the latter case there would be little concern for the effect of the compound on the non-cancer cells, but of course when administering compounds to a patient many additional factors have to be considered including the effect of the compound on normal cells. The specification has not taught that inhibitors of PI kinase activity are generally effective in inhibiting ovarian cancer cell growth without also inhibiting growth of normal ovarian cells as well as other normal cells in the body. Every cell contains a large number of different kinases that could be inhibited by compounds which are general inhibitors of kinases to the obvious detriment of the patient. Consequently, the rationale used in *Fuetterer* is not consistent with the facts of this application. This rejection is therefore maintained.

4. Claims 37-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide sufficient guidance and working examples to enable the skilled artisan to make and use the claimed method of inhibiting the pathological proliferation of ovarian cancer cells in a patient by inhibiting PI kinase activity in cells without undue experimentation. The specification teaches that increased PI-kinase activity might contribute to tumor progression by increasing the rate of cell proliferation and tested this hypothesis by incubating cells from an ovarian cancer cell line with the known PI-kinase inhibitor LY294002. The specification teaches that this assay resulted in a significant decrease in cellular proliferation as measured by thymidine incorporation. This decreased proliferation rate was not observed in cells which had normal PIK3CA copy number. The specification states that these studies suggest that therapeutic agents targeting the PI3-kinase pathway may be effective against ovarian cancers. However, the specification does not describe compounds other than LY294002 which inhibit PI-kinase activity, the specification provide any demonstration that the ability of LY294002 to decrease cell proliferation of an ovarian cancer cell line could be translated to the in vivo environment in a patient. The specification provides no teaching that the in vitro results were known in the art to be predictable when extrapolated into the in vivo environment. Instead the specification states that therapeutic agents which target PI-kinase activity may be effective against ovarian cancer. Shayesteh et al. (Nature Genetics (Jan 1999) 21(1): 99-102.) teach that inhibitors of PI3-kinase will become interesting possible therapeutic agents against ovarian cancer when and if the model that increased PIK3CA copy number and the resulting increase in PI3-kinase activity increase cell proliferation and inhibit apoptosis to allow cells to survive and to genetically evolve

into a more malignant phenotype, and if further studies show that PI3-kinase is activated in ovarian tumors as it seems to be in ovarian cancer cell lines. These teachings establish that extensive additional research is still required to determine whether or not inhibition of PI-kinase is a mechanism that will have an effect on cell proliferation in a patient and that the outcome is unpredictable due to the complexity of the mechanisms involved in cancers such as ovarian cancer and the difficulty in extrapolating in vitro results to the in vivo environment. Consequently, for the reasons set forth above, the skilled artisan would be required to practice undue experimentation to make and use the claimed treatment method.

Response to arguments

The response argues that the invention is not the discovery of PI kinase inhibitors but is instead the discovery that PI kinase plays a role in ovarian cancer proliferation. The response states the inventors concluded that PI kinase inhibitors would have therapeutic benefits based upon the discovery that the PIK3A gene is amplified in ovarian cancer and the PIK3CA protein is overexpressed in cancer cells and that ovarian cells with increased PIK3CA expression also had increased PI kinase activity and finally that a specific inhibitor of PI kinase inhibited ovarian cancer cell proliferation. The response also cited a post filing date publication showing *in vivo* inhibition of ovarian cancer cell proliferation by administration of LY294002 in a mouse model. All of the teachings in the specification and the post filing date cited art has been thoroughly reviewed but is not sufficient to obviate this rejection for the following reasons. First, while the data in the cited Hu et al. paper supports the use of LY294002 as a therapeutic agent for

inhibiting ovarian cell proliferation, this evidence must be submitted in declaration form. The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct as provided by 35 U.S.C. 25 and 18, U.S.C. 1001. In *Ex parte Gray (*10 USPQ2d 1923) the Courts held that conclusory statements made in publications could not substitute for a declaratory evidence filed under 37 CFR 1.132. Furthermore, in *ex parte Ishizaka (*BdPatApp&Int 24 USPQ2d 1621), the Courts stated that 37 CFR 1.132 does not recognize the use of a publication as a substitute for a declaration. Consequently, a Declaration filed under 37 CFR 1.132 sworn by at least one of the instant inventors which cites explains the relevant parts of the Ma et al. And Shayesteh et al. publications would be sufficient to overcome this rejection.

Second, the teachings in the specification do not support the use of PK inhibitors in general for treating ovarian cancer because neither the specification nor the art supports a correlation between generic inhibition of PI kinase activity and effective therapeutic benefits of such inhibitors in patients with ovarian cancer. The specification and the art teach one very specific flavanoid compound which functions PI kinase inhibitor by competitively and reversibly binding to the ATP binding site of the kinase. Other inhibitors which are encompassed by claims 37 and 38 include compounds which would effect the activity of phosphorylating a substrate by binding to a different site on the enzyme or which permanently inactivate the enzyme. Because there are innumerable kinases in the normal cells of a patient, many of the possible "PI kinase inhibitors" would be expected to have harmful side effects on the patient. The specification has

not provided guidance to the skilled artisan to determine the structural features of PI kinase inhibitors which result in the dual function of inhibiting PI kinase activity to then inhibit proliferation of the ovarian cancer cells. The specification has not taught that general inhibition of PI kinase is correlated to selective inhibition of ovarian cancer cell proliferation. Such a teachings would require data showing that a number of structurally diverse compounds capable of inhibiting PI kinase activity also inhibited ovarian cancer cell proliferation without killing normal cells. The results of such an analysis is highly unpredictable because the only exemplified compound was a specific compound already known to have antiproliferative activity on other cancer cells and because LY294002 exerts is effect on PI kinase is a very specific manner which other PI kinase inhibitors would not be expected to have. Therefore, for these reasons undue experimentation would be required to use the broadly claimed method since the specification has not established that generic inhibition of PI kinase by any mechanism is effective for treating a patient with ovarian cancer to inhibit cancer cell proliferation.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday-Wednesday from 7:00 am to 2:30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1096.

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

December 12, 2001